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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,490	05/17/2005	Caroline A Genco	BU-096XX	3937

207 7590 03/25/2008

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
03/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,490	GENCO ET AL.	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *2 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6 and 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1, 3(a), 4-6 and 8-12 filed on December 21, 2007 is acknowledged. Group II, claims 2, 3(b) and 7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being to a non-elected invention.

The traversal is on the grounds that Groups I-II are not independent and distinct, therefore the examination of the entire application does not constitute a serious burden. These arguments have been fully considered but are not found to be persuasive for the reasons below:

It should be noted that this application is a national stage (371) application. Under PCT Unity of Invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. The term "special technical features" is defined as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art. The determination is made based on the contents of the claims as interpreted in light of the description and drawings. Rule 13.2, it is proper to destroy unity of invention by showing that the claims are not linked by a special technical feature to form a single inventive concept.

A single general inventive concept must link the claims in the various categories and in this connection the wording above should be carefully noted. The *link between product and process in (A) is that the process must be "specially adapted for the manufacture of" the product.* Similarly, in (B), the apparatus or means claimed must be

"specifically designed for" carrying out the process. Likewise, in (C), the process must be "specially adapted for the manufacture of" the product and the apparatus must be "specifically designed for "carrying out the process. In combinations (A) and (C), the emphasis is on, and the essence of the invention should primarily reside in, the product, whereas in combination (B) the emphasis is on, and the invention should primarily reside in, the process. The inventions of Group II are not specifically *specially adapted* for the product of Group I. Since the product of Group I may include elements that are not required in the methods of Group II the claims are not linked by a "special technical feature". See PCT Rule 13 and MPEP section 1850. Thus, Group I and II are distinct inventions.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each (see MPEP 802.01). In the instant situation, the inventions of Groups I-II are drawn to distinct inventions which are separate products and methods capable of separate manufacture, use or sale as described in the previous Office Action.

Groups I and II are drawn to *different methods* which require *different endpoints*. Clearly different populations of subjects and different goals are involved with the examination of each Group of inventions. Therefore, different searches and issues are involved in the examination of each Group.

For these reasons the lack of unity requirement is deemed to be proper and is therefore made FINAL. Claims 1, 3-6 and 8-12 are under examination.

Specification Objection

2. The specification is objected because of the use of hyperlink on page 9. Hyperlinks can be readily changed and therefore, may not be available to the public. The specification should be reviewed for hyperlinks and the hyperlink must be deleted from the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

3. Claims 3 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis* does not reasonably provide enablement for portions or fragments of killed whole cell *Porphyromonas gingivalis,* the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that killed whole cell *Porphyromonas gingivalis* or arginine specific proteinases derived from *Porphyromonas* gingivalis (e.g. Arg-gingipain or RGP-1, Lys-gingipain) are the most preferred immunogens used in the claimed method (page 9). There is no guidance provided as to which amino acids can be deleted and still have the *Porphyromonas* gingivalis immunogen retain its biological function. Thus, the resulting immunogen could result in a *Porphyromonas* gingivalis immunogen not taught enabled by the specification.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984",* (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Praline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "*Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in an amino acid's sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide's structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polynucleotide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be

made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would not expect any tolerance to multiple deletions. There is no guidance provided in the specification with regard to how one would begin to choose "portions or fragments" of the killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis* that would be effective in the claimed method. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological
- the specification provides essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other polypeptides having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptide that are portions or fragments of killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis* that would be effective in the claimed method, in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of deletions or fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the polypeptide's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3 and 8-9 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 3 and 8-9 recite the claim limitation "immunogenically effective portion of *Porphyromonas gingivalis* ...". It is unclear as to what Applicant intends by this recitation. What amino acids are required such that the *Porphyromonas gingivalis* is immunogenically effective? Clarification/correction is required.

5. Claims 1, 3 and 8-9 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 3 and 8-9 recite the claim limitation "immunogenically effective portion of *Porphyromonas gingivalis* ...". It is unclear as to what Applicant intends by this recitation. What amino acids are required such that the *Porphyromonas gingivalis* is immunogenically effective? Clarification/correction is required.

6. Claims 1, 3 and 8-9 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 3 and 8-9 recite the claim limitation "immunogenically effective portion ...". It is unclear as to what Applicant intends by this recitation. Is this the same as immunogenically effective amount? Clarification/correction is required.

7. Claim 3 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites *unclear* Markush language. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.d. 126 (Comm'r Pat. 1925). It is unclear as to which immunogen or combination of immunogens Applicant is referring. Correction required.

8. Claim 5 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites "wherein said symptom of cardiovascular disease is atherosclerosis...". Atherosclerosis is a cardiovascular disease not a symptom .Correction required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claim 1 is rejected under 35 U.S.C. 102(e) is anticipated by Barr et al *(U.S. Patent No. 7,204,991 B2 published April 17, 2007).*

Independent claim 1 is directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

Barr et al teach methods of administering compositions comprising *Porphyromonas gingivalis* to patients (see the Abstract). Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD). Barr et al teach because of this linkage, compositions comprising *Porphyromonas gingivalis* may

also be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). Barr et al anticipate the claimed invention.

10. Claims 8-12 are rejected under 35 U.S.C. 102(b) is anticipated by Evans et al *(Infection and Immunity, July 1992, Vol. 60, No.7, p. 2926-2935).*

Independent claim 8 is directed to a vaccine against cardiovascular disease comprising a therapeutically effective quantity of am immunogenically effective portion of heat-killed *Porphyromonas gingivalis.*

Evans et al teach a vaccine composition comprising heat-killed whole cells from *Porphyromonas gingivalis* in Freund's incomplete adjuvant (page 2927). Claim limitations such as "said vaccine being effective in preventing or treating atheroma formation" and " said vaccine being effective in preventing or treating atherosclerosis" are being viewed as limitations of intended use. Evan's anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al *(U.S. Patent No. 6,129,917 published October 2000)* in view of Barr et al *(U.S. Patent No. 7,204,991 B2 published April 17, 2007)*.

Independent claim 1 is directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

Potempa et al teach a method of administering to patients immunogenic compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* (see the Abstract). Potempa et al teach that the compositions of the invention may include immunogenic carriers (column 12). Potempa et al teach that compositions of the invention are used to protect animals against *Porphyromonas gingivalis* infections (see the Abstract).

Potempa et al do not teach the claim limitation "treating a patient having a symptom of cardiovascular disease...".

Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD) (column 3).. Barr et al teach because of this linkage, *Porphyromonas gingivalis* may be used to therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* to treat periodontal disease as taught by Potempa et al and cardiovascular disease because Barr et al teach that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). It would be expected, absent evidence to the contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* or whole cell *Porphyromonas gingivalis* would be effective in treating periodontal disease as well as cardiovascular disease.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be

obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis.* It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease. Thus, it would be obvious to use a known product in a method of treating a cardiovascular symptom to treat a known risk factor or symptom that is ready for improvement to yield predictable results.

12. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al *(U.S. Patent No. 6,129,917 published October 2000)* in view of Fletcher et al *(U.S. Patent No. 6,585, 977 B1 published July 1, 2003)*.

Independent claim 1 is directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

Potempa et al teach a method of administering to patients immunogenic compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* (see the Abstract). Potempa et al teach that the compositions of the invention may include immunogenic carriers (column 12). Potempa et al teach that composition of the invention are used to treat periodontal disease (see the Abstract).

Potempa et al do not teach the claim limitation "treating a patient having a symptom of cardiovascular disease...".

Fletcher et al teach that periodontitis (periodontal disease) affects more than 49 million people in the United States and hundreds of millions of people worldwide and has been reported as a risk factor for cardiovascular disease (column 1).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) or the *Porphyromonas gingivalis* mutant to treat periodontal disease as well as cardiovascular disease because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease. Thus, one of ordinary skill in the art would reasonably conclude that treating periodontal disease would reduce the risk of cardiovascular disease. It would be expected, absent evidence to the contrary, that a composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or the *Porphyromonas gingivalis* mutant as taught by Fletcher et al would be effective in treating periodontal disease as well as cardiovascular disease.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be

obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis.* It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease. Thus, it would be obvious to use a known product in a method of treating a cardiovascular symptom to treat a known risk factor or symptom that is ready for improvement to yield predictable results.

14. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al *(U.S. Patent No. 6,129,917 published October 2000)* in view of Barr et al *(U.S. Patent No. 7,204,991 B2 published April 17, 2007)* as applied to claims 1 and 3 and further in view of Strandberg et al *(Arterioscler Thromb Vasc Biol., April 2000, p. 1057-1060).*

Claims 4 and 5 are directed to the method of claim 1, wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

Potempa et al and Barr et al have been described previously.

Potempa et al and Barr et al do not teach claim limitations the method of claim 1, wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals (see the Abstract).

Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder (page 1057). Strandberg et al teach that elevated C-reactive protein have been predicted coronary events in middle-aged women and men (page 1057).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* to periodontal disease and cardiovascular disease (e.g. arthrosclerosis) in patients with elevated C-reactive protein levels because Barr et al teach that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). Also, Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals. It would be expected, absent evidence to the contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or whole cell *Porphyromonas gingivalis* as taught by Barr et al would be effective in treating periodontal disease as well as arthrosclerosis.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as arthrosclerosis. It is known in the art that elevated C-reactive protein is a predictor if cardiovascular events. Thus, it would be obvious to use a known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

15. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al *(U.S. Patent No. 6,129,917 published October 2000)* in view of Fletcher et al *(U.S. Patent No. 6,585, 977 B1 published July 1, 2003)* as applied to claims 1 and 3 and further in view of Strandberg et al *(Arterioscler Thromb Vasc Biol., April 2000, p. 1057-1060)*.

Claims 4 and 5 are directed to the method of claim 1, wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

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reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals (see the Abstract). Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder (page 1057). Strandberg et al teach that elevated C-reactive protein have been predicted coronary events in middle-aged women and men (page 1057).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* or an immunogenic composition comprising the *Porphyromonas gingivalis* mutant of Fletcher et al to treat periodontal disease and cardiovascular disease (e.g. arthrosclerosis) in patients with elevated C-reactive protein levels because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease. Thus, one of ordinary skill in the art would reasonably conclude that treating periodontal disease would reduce the risk of cardiovascular disease. It would be expected, absent evidence to the contrary, that a composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or the *Porphyromonas gingivalis* mutant as taught by Fletcher et al would be effective in treating periodontal disease as well as cardiovascular disease. Also, Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular

disease in middle aged individuals. It would be expected, absent evidence to the contrary, that compositions comprising the *Porphyromonas gingivalis* mutant and the *Porphyromonas gingivalis* compositions would be effective in treating periodontal disease as well as arthrosclerosis.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as arthrosclerosis. It is known in the art that elevated C-reactive protein is a predictor if cardiovascular events. Thus, it would be obvious to use a known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

16. Claim 6 is rejected under 35 U.S.C. 103(a) as patentable over Potempa et al Barr et al and Strandberg et al as applied to claims 1 and 3-5 above and further in view of P. Amarenco et al *(New England Journal of Medicine, May 9, 1996).*

Claim 6 is directed to the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

Potempa et al Barr et al and Strandberg et al have been described previously.

Potempa et al Barr et al and Strandberg et al do not teach the claim limitation the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

P. Amarenco et al teach that atherosclerotic disease of the aortic arch is a risk factor for recurrent ischemic stroke (cardiovascular disease)(see the Title and the Abstract). P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events (see the Abstract).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* to treat periodontal disease and cardiovascular disease (e.g. arthrosclerosis) in patients with elevated C-reactive protein levels and atheroma formation in the aortic arch because Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD) and that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals and P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events. It would be expected, absent evidence to the

contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or whole cell *Porphyromonas gingivalis* as taught by Barr et al would be effective in treating periodontal disease as well as arthrosclerosis in patients that have elevated C-reactive proteins and atheroma formation in the aortic arch based on the combination of teachings provided in the prior art.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as arthrosclerosis. It is also known in the art that elevated C-reactive protein and atheroma formation in the aortic arch are predictors of cardiovascular events. Thus, it would be obvious to use a known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

17. Claim 6 is rejected under 35 U.S.C. 103(a) as patentable over Potempa et al , Fletcher et al and Strandberg et al as applied to claims 1 and 3-5 above and further in view of P. Amarenco et al *(New England Journal of Medicine, May 9, 1996).*

Claim 6 is directed to the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

Potempa et al, Fletcher et al and Strandberg et al have been described previously.

Potempa et al, Fletcher et al and Strandberg et do not teach the claim limitation the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

P. Amarenco et al teach that atherosclerotic disease of the aortic arch is a risk factor for recurrent ischemic stroke (cardiovascular disease)(see the Title and the Abstract). P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events (see the Abstract).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition *Porphyromonas gingivalis* mutant or the *Porphyromonas gingivalis* to treat periodontal disease and cardiovascular disease (e.g. arthrosclerosis) in patients with elevated c-reactive protein levels and atheroma formation in the aortic arch because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease. Thus, one of ordinary skill in the art would reasonably conclude that treating periodontal disease would reduce the risk of cardiovascular disease. Strandberg et al teach that C-reactive protein (CRP) reflects

inflammation and predicts cardiovascular disease in middle aged individuals and P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events. It would be expected, absent evidence to the contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or *Porphyromonas gingivalis* mutant as taught by Fletcher et al would be effective in treating periodontal disease as well as arthrosclerosis in patients that have elevated c-reactive proteins and atheroma formation in the aortic arch based on the combination of teachings provided in the prior art.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as arthrosclerosis. It is also known in the art that elevated C-reactive protein and atheroma formation in the aortic arch are predictors of cardiovascular events. Thus, it would be obvious to use a

known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

Status of Claims

18. No claims are allowed.

Conclusion

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
March 10, 2008